REMARKS

Claims 23-37 presently appear in this case. No claims have been allowed. The official action of April 27, 2007, has now been carefully studied. Reconsideration and allowance are hereby respectfully urged.

Briefly, the present invention relates to the inhibition of neuronal degeneration or promotion of nerve regeneration of an individual suffering from an injury, disorder or disease of the CNS or PNS or for the treatment of an injury, disorder or disease of the CNS or PNS, particularly, spinal cord injury. The method involves administering an effective amount of antigen presenting cells that have been pulsed with a nervous system specific antigen or an analog thereof, or a peptide derived from an (NS)-specific antigen or from an analog thereof, or an analog or derivative of said peptide.

Claims 23-37 have been rejected under 35 U.S.C. 112, first paragraph, on the ground that the specification, while being enabling for administration of dendritic cells pulsed with residues 87-99 of myelin basic protein or the same peptide wherein the lysine at residue 91 was replaced with alanine [A91] with subsequent attenuation of locomotion symptoms in patients with spinal cord injury, does not reasonably provide enablement for administration of cells

pulsed with any and all NS-specific antigen or analog or derivative thereof as broadly claimed in independent claims 23, 31 and 36, or for prevention of neuronal degeneration as set forth in claim 23, or for treatment of diseases or conditions as recited in claim 31, or for treatment of the specific diseases and conditions recited in claims 32-33. The Examiner recites the eight factors considered in *In re Wands* when determining if the disclosure satisfies the enablement rejection and cites Yoles et al. (2001, *J. Neurosc.* 21:3740-48) to show that spinal cord injury is characterized by a period of initial damage and injury, followed by secondary cell loss which affects neurons that had survived the initial trauma and that steroids and anti-inflammatory cytokines are either beneficial or harmful to the injury depending on when they are administered. This leads the examiner to the conclusion that this is a complex field in which it is difficult to extrapolate from specific findings as to therapeutic efficacy of compounds to more general conclusions about related compounds or even to different dosing and treatment regimens. In support of the rejection, the examiner alleges that Huang et al. teaches inducing tolerance to EAE in rats treated with dendritic cells pulsed with MBP 68-86. The examiner states that the reference clearly shows that administering dendritic cells pulsed with other nervous-system

specific antigens (MOG 35-55 or PLP 139-151) is not successful in this same paradigm. The examiner concludes that, as the specification offers only two working examples of ameliorating symptoms by administering cells pulsed with nervous-system specific antigens, the prior art indicates other nervous-system specific antigens will not work, and the specification offers no guidance as to how to overcome this finding, the claimed methods are not enabled over the full scope of nervous-system specific antigens as recited in claims 23, 31 and 36. This rejection is respectfully traversed.

First, with respect to the teachings of Huang, the results therein show that dendritic cells pulsed with MOG or PLP peptide did not suppress development of EAE induced by MBP 68-86, while MBP-peptide pulsed cells did, and accordingly, the authors concluded that "[dendritic cell]-mediated tolerance is antigen-specific." Thus, the examiner's conclusions about Huang are not correct as the Huang paper is directed to treatment of EAE, a model for a human autoimmune disease, while the present invention is not directed to treatment of autoimmune diseases. It is directed to the treatment of secondary neuronal degeneration that follows a primary injury in the CNS or PNS, for example, an injury in the spinal cord, or that which follows a disease, for example, glaucoma, Parkinson's disease, amyotrophic lateral sclerosis,

or Huntington's disease. Thus, for this reason alone, the Huang paper is not suitable evidence against the enablement of the present application.

Moreover, on closer consideration, it can be seen that the examiner has drawn the wrong conclusion from the Huang paper with respect to the present application. The reason that the MOG and PLP peptides were not efficient in suppressing development of EAE was that the disease was induced by an MBP peptide. Contrary to Huang, in the present invention the damage to the nervous system is induced by injury to the spinal cord which exposes the immune system to all nervous specific antigens, including MOG and PLP, that would therefore have the same potential beneficial effect as the MBP peptide.

The examiner also contends lack of enablement for prevention of neuronal degeneration as recited in claim 23. Claim 23 has now been amended so as not to read on prevention, thus obviating this objection.

The examiner also argues that there is no enablement in the specification for treatment of all diseases encompassed by claim 31 and as recited in claims 32 and 33, stating that there is no reason to believe that the treatments would be useful in treatment of the diseases in claim 32, as they do not share a common mechanism of action. However, the art is aware that the same mediators are involved in secondary

neuronal degeneration, regardless of whether the primary insult is an acute injury or the chronic degeneration of a disease. As evidence of this conclusion, the examiner's attention is invited to the following three attached references:

> (1)SCHWARTZ, M. et al., "A Common Vaccine for Fighting Neurodegenerative Disorders: Recharging Immunity for Homeostasis", TRENDS in Pharmacological Sciences, 25:407-412 (2004)
>
> (2) FRIEDLANDER, R.M. "Apoptosis and Caspases in Neurodegenerative Diseases" N Engl J Med, 348:1365-75 (2003)
>
> (3) VAJDA, F.J.E. "Neuroprotection and neurodegenerative disease" J Clin Neurosci, 9:4-8 (2002)

Friedlander is a review that very clearly includes stroke, brain trauma, spinal cord injury, ALS, Parkinson's disease, etc., in the same category of neurodegenerative diseases. Vajda is another review that describes pathological pathways in five different neurodegenerative diseases. It is believed that these reviews confirm the statements in Schwartz and Kipnis that the same factors, i.e, the same mediators, are involved in secondary neuronal degeneration, regardless of whether the primary insult is an acute injury or the chronic degeneration of a disease. For all of these reasons, given the results that the examiner considers convincing in the present specification with respect to dendritic cells and spinal cord injury and what is known about the relationship of

the various conditions claimed and the other explanations provided herein, those of ordinary skill in the art would be able to practice the full scope of the present invention without undue experimentation. Reconsideration and withdrawal of this rejection is therefore respectfully urged.

Claims 23-28, 31-34 and 36 have been rejected under 35 U.S.C. 102(b) as being anticipated by the earlier US 5,800,812 patent from the laboratory of the present inventors (the '812 patent). According to the examiner, the '812 patent teaches obtaining antigen-presenting cells, including dendritic cells and culturing them in the presence of nerve segments. The examiner takes the position that nerve segments reasonably meet the limitation of "a nervous system specific antigen" as recited in claims 23, 31 and 36. This rejection is respectfully traversed.

Nerve segments do not reasonably meet the limitation of "a nervous system specific antigen." Submitted herewith is a definition of "antigen" from Kahl, "The Dictionary of Gene Technology: Genomics, Transcriptomics, Proteomics", 3rd Edition, 2004, Wiley-VCH Verlag GmBH & Co. KGaA, Weinheim, Germany, which at page 53 defines antigen as:

> A chemical compound (e.g. a protein) or a specific structural feature of it, which elicits the production of a specific antibody if introduced into an immunologically reactive organism. The

> antigen is bound by the antibody or a T cell receptor.

See also the Wikipedia entry for "antigen," also submitted herewith, which defines it as "a molecule that stimulates an immune response." That an antigen is a molecule and not a tissue is fully consistent with the examples in the present specification given at page 17, lines 16-25. A nerve segment is not reasonably encompassed by that definition. As the '812 patent does not teach pulsing with an antigen, reconsideration and withdrawal of this rejection are respectfully urged.

Claims 23-28, 31-34 and 36 have also been rejected under 35 U.S.C. 102(a) and 102(e) as being anticipated by US patent 6,267,955 (the '955 patent), also from the laboratory of the present inventors. The examiner also relies on this patent for its teaching of culturing dendritic cells in the presence of nerve segments. This rejection is respectfully traversed.

The '955 patent suffers from the same deficiencies as the '812 patent discussed above. A nerve segment is not an antigen as is required by the present claims. It is not a molecule, but a piece of tissue. Accordingly, the '955 patent does not anticipate any of the present claims for the same reasons as discussed above for the '812 patent. Reconsideration and withdrawal of this rejection are therefore respectfully urged.

Claims 23 and 29 have been rejected under 35 U.S.C. 102(b) as being anticipated by Huang. The examiner states that Huang teaches pulsing dendritic cells with MBP peptide 68-86 and administering the cells to rats to induce protection against subsequent induction of EAE, which is a degenerative disease. This rejection is respectfully traversed.

Claim 23 has now been amended to remove reference to prevention. Accordingly, no reading of Huang can be considered to anticipate claim 23 or any of the claims dependent therefrom as presently written. Reconsideration and withdrawal of this rejection are also respectfully urged.

Claims 23-28, 31 and 35 have been rejected under 35 U.S.C. 102(b) as being anticipated by Ben-Nun. The examiner states that Ben-Nun teaches pulsing antigen-presenting cells, specifically macrophages, with MBP and subsequent administration to mice that had already had EAE induced. The examiner states that the procedure is sufficient to attenuate the development of EAE. The examiner states that, as the reference teaches administration of the antigen-presenting cells that had been pulsed with MBP, an NS-specific antigen, and subsequent attenuation of severity of symptoms of EAE, it fairly anticipates claims 23 and 31. This rejection is respectfully traversed.

Ben-Nun requires intraperitoneal (ip) administration (see the first paragraph of the discussion on page 360). Iv administration does not work. Ben-Nun speculates at the first paragraph of section 3.2, on page 359, that MBP-pulsed macrophage inoculated into the peritoneal cavity attract the MBP-specific pathogenic T cells there and hinder their migration to the CNS. Thus, it is clear that Ben-Nun requires the local administration of the pulsed microphages to the peritoneal cavity. This is not a means of systemic administration, but a means of local administration away from the CNS so as to direct the disease causing T cells to the peritoneal cavity.

The present invention works in quite the opposite way. It is desired for the pulsed cells to arrive at the site of injury or disease, as this is what causes the beneficial results.

In order to clarify this difference, the present claims have now been amended to specify that the cells are administrated locally at the site of injury or disease or systemically. Accordingly, these claims are not anticipated by Ben-Nun. Reconsideration and withdrawal of this rejection are also respectfully urged.

Claims 23, 28, 31-32 and 34-36 have been rejected under 35 U.S.C. 103(a), as being unpatentable over Ben-Nun in

view of Hauben, Popovich, and Schwartz (2001). The examiner states that the teachings of Ben-Nun have been discussed above, but the examiner recognizes that Ben-Nun does not teach treatment of spinal cord injury or local administration, as recited in claim 34. The examiner states that Hauben teaches treatment of spinal cord injury by administration of T cells that recognize the NS-specific antigen MBP, and that Popovich teaches the similar natures and mechanisms of EAE and spinal cord injury. The examiner states that Schwartz teaches the concept of protective autoimmunity. Thus, the examiner considers it obvious to administer antigen-presenting cells that have been pulsed with MBP, as taught by Ben-Nun, for treatment of spinal cord injury. This rejection is respectfully traversed.

As discussed above, Ben-Nun teaches away from the present invention as it requires that the pulsed cells not reach the site of the injury. Ben-Nun teaches that the cells must be administered to the peritoneal cavity, where there is no CNS or PNS injury, so as to draw the T cells away from the injury. Hauben and Schwartz teach quite a different mechanism. The protective autoimmunity of Schwartz requires that the T cells reach the site of injury or disease. Nothing in Popovich would suggest why the disclosure of Ben-Nun might be used to treat spinal cord injury or how administration to

the peritoneal cavity would possibly treat spinal cord injury. Certainly, there is no suggestion to administer the cells to the site of injury, particularly in view of Ben-Nun's requirement that the cells do not reach the site of the injury. Accordingly, none of the present claims are made obvious by the combination of references cited by the examiner. Reconsideration and withdrawal of this rejection is also respectfully urged.

Claims 23, 28, 31-32 and 34-37 have been rejected under 35 U.S.C. 103(a), as being unpatentable over Ben-Nun in view of Hauben, Popovich and Schwartz and further in view of Gaur. The examiner states that Gaur teaches the protein SEQ ID NO:4 as recited in claim 37. The examiner considers it obvious to pulse the antigen presenting cells with the protein of SEQ ID NO:4. This rejection is respectfully traversed.

Even if the cells of Ben-Nun were pulsed with SEQ ID NO:4, the cells would still be administered intraperotneally, according to the teachings of Ben-Nun, and therefore would not meet the requirement of claim 36 that the cells be administered systemically or locally at the site of injury. Accordingly, as Gaur adds nothing to the deficiency's of Ben-nun, Hauben, Popovich and Schwartz as discussed above, reconsideration and withdrawal of this rejection are respectfully urged.

Claims 23-29 have been rejected under 35 U.S.C. 103(a), as being unpatentable over Huang in view of Link. The examiner states the reasons Huang anticipates claims 23, 28 and 29 have been discussed above, but the examiner recognizes that Huang does not teach administration of human dendritic cells, autologous to the patient in need, obtained from skin, spleen, thymus, marrow, lymph nodes, or peripheral blood. The examiner states that Link teaches administration of autologous dendritic cells that have been exposed to a selected biological milieu *in vitro* and then returning the cells to the same patient. The examiner considers it to have been obvious to modify the method of Huang to use autologous dendritic cells to treat human patients as suggested by Link with a reasonable expectation of success. This rejection is respectfully traversed.

As discussed above, claim 23 has been amended to require that the cells be administered to an individual suffering from an injury, disorder or disease of the CNS or PNS. Huang teaches only preventive treatment. Link supplies none of the deficiencies of Huang in this regard. Thus, it would not have been obvious to anyone of ordinary skill in the art reading Huang or Link to administer pulsed cells to an individual suffering from an injury, disorder or disease of

the CNS or PNS. Reconsideration and withdrawal of this rejection are also respectfully urged.

Claims 23-28, 31-34, and 36 have been rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-3, 6-28, 31-34, and 37-46 of US patent no. 6,267,955, The examiner states that the claims are not patentably distinct because in each case the claims are drawn to methods of administering antigen-presenting cells that have been pulsed with nervous system specific antigens for treatment of diseases, including those diseases characterized by axonal damage. This rejection is respectfully traversed.

As discussed hereinabove, with respect to the anticipation rejection over the same patent, nerve segments are not the same as a nervous system specific antigen. An antigen is a molecule not a tissue. Thus, the claims are neither anticipated nor are they directed to the same invention. Accordingly, this double patenting rejection must fall for the same reasons as discussed above with respect to the anticipation rejection. Reconsideration and withdrawal of the double patenting rejection is therefore respectfully urged.

Claims 23-28, 31-34 and 36 have been rejected on the ground of nonstatutory obviousness-type double patenting as

being unpatentable over claims 1-26 of US patent no. 5,800,812. The examiner considers that the claims are not patentably distinct for the same reasons as discussed with respect to the claims of the '955 patent. This rejection is respectfully traversed.

As discussed above with respect to the anticipation rejection of the '812 patent and with respect to the anticipation and double patenting rejections of the '955 patent, nerve segments are not antigens and therefore claims of the '812 patent are not directed to the same invention as the present claims. Accordingly, the double patenting rejection must fall for the same reasons as discussed above with respect to the anticipation rejection. Reconsideration and withdrawal of this rejection are therefore respectfully urged.

The examiner states that because claims of the present application are not patentably distinct from claims of the commonly assigned '955 and '812 patents, the examiner must make a determination whether those applications qualify as prior art under 35 U.S.C. 102(e), (f), or (g). The examiner thus requires applicant to state which application was the prior invention.

First of all, there is no conflicting subject matter for the reasons discussed above. Secondly, all of the patents

are owned by the same entity and therefore no 35 U.S.C. 103(a) rejection based on 102(f), (g), or (e) are applicable. Reconsideration and withdrawal of this requirement are therefore respectfully urged.

It is submitted that all the claims now present in the case clearly define over the references of record and fully comply with 35 U.S.C. 112. Reconsideration and allowance are therefore earnestly solicited.

Respectfully submitted,

BROWDY AND NEIMARK, P.L.L.C.
Attorneys for Applicant(s)

By /rlb/
Roger L. Browdy
Registration No. 25,618

RLB:jmd
Telephone No.: (202) 628-5197
Facsimile No.: (202) 737-3528
G:\BN\B\BENA\Eis-Schwartz37\pto\2007-10-29Amd.doc